Complete Summary

GUIDELINE TITLE

Antithrombotic therapy. A national clinical guideline.

BIBLIOGRAPHIC SOURCE(S)

Antithrombotic therapy. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 1999. 70 p. (SIGN publication; no. 36). [186 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Arterial, cardiac, and venous thromboembolism
- Anticoagulant overdose and bleeding during anticoagulant therapy

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Hematology

Internal Medicine
Neurology
Nursing
Pulmonary Medicine
Surgery

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assist individual health boards, general practitioners, hospital departments and hospitals to produce local guidelines for:

- Identification of patients at increased risk for arterial thromboembolism, or who have acute thromboembolism
- Routine administration and monitoring of appropriate, effective antithrombotic prophylaxis and treatment in such patients
- Prevention and management of anticoagulant overdosage or bleeding during anticoagulant therapy

TARGET POPULATION

- Patients with arterial, cardiac, and venous thromboembolism, including pulmonary embolism and deep vein thrombosis
- Patients at risk for arterial or cardiac thromboembolism, including patients with atrial fibrillation, those with mechanical heart valves, those with peripheral arterial disease, and those at risk for recurring myocardial infarction or stroke
- Patients with anticoagulant overdose or those with bleeding complications from use of anticoagulants

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Initial Assessment

A. Acute venous thromboembolism (deep venous embolism or pulmonary embolism)
    1. Assessment using evaluation of predisposing factors, symptoms and signs, and clinical prediction guidelines
    2. Diagnostic imaging with venography, ultrasound, ventilation-perfusion lung scanning, spiral computed tomography angiography or pulmonary angiography, objective test, and echocardiography
B. Atrial fibrillation
    1. Echocardiography
    2. Assessment for risk factors for systemic thromboembolism
C. Cerebrovascular disease

1. Computed tomography brain scanning

Treatment/Management of Thromboembolism

A. General management principles
    1. Antiplatelet therapy including aspirin, clopidogrel, and dipyridamole. both as acute therapy and as long-term prophylaxis
    2. Anticoagulant therapy including heparins (unfractionated heparin and low-molecular-weight heparin) and warfarin, both in acute therapy and as long-term prophylaxis
    3. Thrombolytic therapy including streptokinase, anistreplase, and tissue plasminogen activator (alteplase)
    4. Baseline coagulation screen and thrombophilia screen; baseline blood and platelet count; and baseline urea, electrolytes, and liver function tests prior to starting anticoagulant therapy
    5. Monitoring of activated partial thromboplastin time (APTT) and international normalized ratio of prothrombin time (INR) to achieve optimal targets
    6. Monitoring of platelet count to detect heparin-induced thrombocytopenia
    7. Monitoring of bone density in heparin-treated patients at risk for fractures
    8. Identification and management of patients with congenital or acquired thrombophilias
    9. Reversal of oral anticoagulant therapy in patients with bleeding or high international normalized ratio (use of vitamin K1, factor IX complex, factor VII concentrate)
B. Additional treatment/management in acute venous thromboembolism
    1. Cardiorespiratory resuscitation
    2. Percutaneous catheter thrombus fragmentation
    3. Pulmonary embolectomy
    4. Leg elevation
    5. Venous thrombectomy
    6. Graduated elastic compression stocking
    7. Inferior vena cava (IVC) filter insertion (e.g., Greenfield caval filter)
C. Additional treatment/management in atrial fibrillation
    1. Cardioversion
D. Additional treatment/management in ischaemic heart disease
    1. Platelet glycoprotein IIb/IIIa inhibitors (e.g. abciximab)

MAJOR OUTCOMES CONSIDERED

- Positive and negative predictive value of diagnostic tests for thromboembolism
- Relative risk of recurrent thromboembolic events
- Rate of major bleeding episodes, including intracranial bleeding
- Disability
- Mortality
- Morbidity
- Risk of myocardial infarction, stroke, systemic embolism, and other cardiovascular events
- Rate of progression of atherosclerosis

- Risk of peripheral arterial surgery
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Statements of Evidence:

Ia: Evidence obtained from meta-analysis of randomized controlled trials.

Ib: Evidence obtained from at least one randomized controlled trial.

IIa: Evidence obtained from at least one well-designed controlled study without randomization.

IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study.

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Scottish Intercollegiate Guidelines Network (SIGN) carries out comprehensive systematic reviews of the literature using customized search strategies applied to a number of electronic databases and the Internet. This is often an iterative process whereby the guideline development group will carry out a search for existing guidelines and systematic reviews in the first instance and, after the results of this search have been evaluated, the questions driving the search may be redefined and focused before proceeding to identify lower levels of evidence.

Once papers have been selected as potential sources of evidence, the methodology used in each study is assessed to ensure its validity. SIGN has developed checklists to aid guideline developers to critically evaluate the methodology of different types of study design. The result of this assessment will affect the level of evidence allocated to the paper, which in turn will influence the grade of recommendation it supports.

Additional details can be found in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [UK]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50]). Available from the SIGN Web site.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The process for synthesizing the evidence base to form graded guideline recommendations is illustrated in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [UK]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50], available from the SIGN website.

Evidence tables should be compiled, summarizing all the validated studies identified from the systematic literature review relating to each key question. These evidence tables form an important part of the guideline development record and ensure that the basis of the guideline development group's recommendations is transparent.

In order to address how the guideline developer was able to arrive at their recommendations given the evidence they had to base them on, SIGN has introduced the concept of considered judgement.

Under the heading of considered judgement, guideline development groups are expected to summarise their view of the total body of evidence covered by each evidence table. This summary view is expected to cover the following aspects:

- Quantity, quality, and consistency of evidence
- Generalisability of study findings
- Applicability to the target population of the guideline
- Clinical impact (i.e., the extent of the impact on the target patient population, and the resources need to treat them.)

Guideline development groups are provided with a pro forma in which to record the main points from their considered judgement. Once they have considered these issues, the group are asked to summarise their view of the evidence and assign a level of evidence to it, before going on to derive a graded recommendation.

The assignment of a level of evidence should involve all those on a particular guideline development group or subgroup involved with reviewing the evidence in relation to each specific question. The allocation of the associated grade of recommendation should involve participation of all members of the guideline development group. Where the guideline development group is unable to agree a unanimous recommendation, the difference of opinion should be formally recorded and the reason for dissent noted.

The recommendation grading system is intended to place greater weight on the quality of the evidence supporting each recommendation, and to emphasise that the body of evidence should be considered as a whole, and not rely on a single study to support each recommendation. It is also intended to allow more weight to be given to recommendations supported by good quality observational studies where randomised controlled trials (RCTs) are not available for practical or ethical reasons. Through the considered judgement process guideline developers are also able to downgrade a recommendation where they think the evidence is not generalisable, not directly applicable to the target population, or for other reasons is perceived as being weaker than a simple evaluation of the methodology would suggest.

On occasion, there is an important practical point that the guideline developer may wish to emphasise but for which there is not, nor is their likely to be, any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline as "good practice points." It must be emphasized that these are not an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

Grade A: Requires at least one randomized controlled trial (RCT) as part of a body of literature of overall good quality and consistency addressing the specific recommendation (Evidence levels Ia, Ib).

Grade B: Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (Evidence levels IIa, IIb, III).

Grade C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (Evidence level IV).

Good Practice Points: Recommended best practice based on the clinical experience of the guideline development group.

COST ANALYSIS

The guideline developers reviewed the cost-effectiveness of antithrombotic therapy, antiplatelet therapy, and anticoagulant therapy.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

1. National open meeting discusses the draft recommendations of each guideline.
2. Independent expert referees review the guideline.
3. The Scottish Intercollegiate Guidelines Network (SIGN) Editorial Board reviews the guideline and summary of peer reviewers' comments.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the Scottish Intercollegiate Guidelines Network (SIGN) and National Guideline Clearinghouse (NGC): In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

The strength of recommendation grading (A-C) and level of evidence (Ia-IV) are defined at the end of the "Major Recommendations" field.

Venous Thromboembolism

Diagnosis of Acute Venous Thromboembolism

C - Diagnostic imaging should be performed expeditiously (within 24 hours if possible) in patients with suspected deep vein thrombosis (venography, ultrasound) or pulmonary embolism (e.g., ventilation-perfusion lung scanning) to minimise exposure to the risks of inappropriate continued full-dose anticoagulation in those patients in whom venous thromboembolism is not confirmed.

B - In all patients with clinically-suspected deep vein thrombosis, the diagnosis should be confirmed or excluded by diagnostic imaging, either:

- Non-invasive testing by ultrasound (compression or Duplex scanning), followed by contrast venography if negative to detect calf deep vein thrombosis and nonocclusive proximal deep vein thrombosis; or
- Contrast venography (which detects both calf and proximal deep vein thrombosis); or

- Serial (repeat after seven days) non-invasive testing by ultrasound (compression or Duplex scanning) to detect proximal extension of calf deep vein thrombosis.

B - A single negative ultrasound may be sufficient to exclude deep vein thrombosis in patients with low clinical pre-test probability and/or a normal fibrin D-dimer assay.

B - In all patients with clinically suspected pulmonary embolism, the diagnosis should be confirmed or excluded by an objective test.

Heparin in Acute Treatment of Deep Vein Thrombosis or Pulmonary Embolism

A - Outpatients with clinically suspected deep vein thrombosis or pulmonary embolism should be referred to hospital for diagnosis and consideration of initial anticoagulation with heparin, to reduce the risk of further venous thromboembolic events which are often fatal or disabling.

A - In clinically-suspected deep vein thrombosis or pulmonary embolism, heparin should be commenced (unless strongly contraindicated) until the diagnosis is excluded by diagnostic imaging.

B - Monitoring of the activated partial thromboplastin time ratio should be performed expeditiously in patients receiving unfractionated heparin, and heparin doses adjusted according to a local protocol, to achieve the therapeutic target range (usually 1.5 to 2.5) within 24 hours.

C - The platelet count should be monitored to detect heparin-induced thrombocytopenia (as stipulated by the Committee on Safety of Medicines).

A - Subcutaneous unfractionated heparin is an effective alternative to intravenous unfractionated heparin for the initial treatment of deep vein thrombosis.

A - Low molecular weight heparins are effective alternative treatment to unfractionated heparin for deep vein thrombosis and pulmonary embolism.

Oral Anticoagulants in Acute and Maintenance Treatment of Deep Vein Thrombosis or Pulmonary Embolism

A - Following initial heparinisation in patients with deep vein thrombosis or pulmonary embolism, maintenance of anticoagulation with oral anticoagulants is recommended in non-pregnant patients.

A - The optimal target international normalized ratio of prothrombin time during oral anticoagulant therapy for a first episode of venous thromboembolism is 2.5, range 2.0 to 3.0.

C - When oral anticoagulant therapy is initiated for treatment of acute deep vein thrombosis or pulmonary embolism it should be overlapped with heparin therapy

for 4 to 6 days and until the international normalized ratio of prothrombin time is >2.0 on two consecutive days.

A - Early institution of oral anticoagulants is recommended in most patients.

A - The routine recommended duration of oral anticoagulant therapy following a first episode of deep vein thrombosis or pulmonary embolism is for at least three months.

C - At three months, patients should be assessed for continuing risk factors (e.g., idiopathic, premature or familial presentation; thrombophilias; malignancy; chronic infection; inflammatory bowel disease; nephrotic syndrome; thromboembolic pulmonary hypertension).

C - The presence of continuing risk factors suggests consideration of anticoagulation long term, or until such risk factors resolve.

Heparins in Maintenance Treatment of Deep Vein Thrombosis or Pulmonary Embolism

A - Adjusted-dose subcutaneous heparin may be considered as an alternative therapy for patients in whom oral anticoagulants are either contraindicated (e.g., pregnancy), inconvenient (e.g., distance from monitoring facilities) or ineffective (e.g., in some cancer patients).

Other Antithrombotic Therapies in Treatment of Deep Vein Thrombosis or Pulmonary Embolism

C - In patients with massive pulmonary embolism, cardiorespiratory resuscitation and support, urgent intravenous heparinisation, and urgent confirmation of the diagnosis by echocardiography, spiral computed tomography, pulmonary angiography, or lung scanning are appropriate.

C - Thrombolytic therapy, percutaneous catheter thrombus fragmentation, or pulmonary embolectomy may each be considered, according to local facilities and expertise.

C - In patients with massive deep vein thrombosis, leg elevation to reduce oedema, urgent intravenous heparinisation, and urgent confirmation of the diagnosis by venography or ultrasound are appropriate.

C - Thrombolytic therapy or venous thrombectomy may be considered in patients with threatened venous gangrene.

C - In acute non-massive deep vein thrombosis, leg oedema can be reduced initially by leg elevation, and recurrent oedema minimised by mobilisation with a graduated elastic compression stocking and intermittent leg elevation.

C - If therapeutic anticoagulation is contraindicated (e.g., due to high bleeding risk), inferior vena cava (IVC) filter insertion (e.g., with a Greenfield caval filter) should be considered.

A - Graduated elastic compression stockings should be worn on the affected leg following proximal deep vein thrombosis for at least two years to reduce the incidence of severe post-thrombotic leg syndrome.

Identification and Management of Patients with Chronic Increased Risk (Thrombophilias)

C - Screening for congenital or acquired thrombophilias (deficiencies of antithrombin, protein C or protein S; activated protein C resistance which is usually due to the coagulation factor V Leiden mutation; the prothrombin 20210A mutation; lupus anti-coagulants which are usually antiphospholipid antibodies) is recommended in selected groups.

C - Patients with such thrombophilias should be referred to consultant haematologists or centres with expertise in management of thrombophilia, which includes:

- Genetic counseling
- General education and advice on the additive risks of obesity and oestrogen containing oral contraceptives or hormone replacement therapy
- Prophylaxis: either short term anticoagulant prophylaxis during periods of increased risk of deep vein thrombosis or pulmonary embolism (pregnancy, puerperium, trauma, surgery, or medical illness) or in selected patients long term anticoagulation with warfarin.

Atrial Fibrillation: Prophylaxis of Systemic Embolism

Efficacy of Warfarin and Aspirin as Antithrombotic Prophylaxis

B - In all patients with atrial fibrillation, risk factors for systemic thromboembolism should be assessed routinely.

A - Lower risk patients (annual stroke rate under 3%) should be given no antithrombotic prophylaxis , unless aspirin (75 to 300 mg/day) is given for other indications.

A - Higher risk patients (annual stroke rate over 3%) should be considered for warfarin at a target international normalized ratio [INR] of prothrombin time of 2.5 (range 2.0 to 3.0). The balance of risks and benefits of warfarin should be assessed and discussed with the patient, and reassessed annually in individual higher risk patients: aspirin may be a safer alternative to warfarin in some of these patients.

A - Anticoagulant therapy after an acute cerebral ischaemic event should be delayed until most of the deficit has resolved or, in the case of more severe strokes, more than two weeks has elapsed.

Higher Risk Groups

A - Warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) should be considered for antithrombotic prophylaxis in patients with

non-valvular atrial fibrillation and a history of previous ischaemic stroke or transient cerebral ischaemic attack.

A - If warfarin is declined, or contraindicated by increased risk of bleeding, aspirin (75 to 300 mg/day) should be considered, but is less effective than warfarin.

A - Warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) should be considered for antithrombotic prophylaxis in patients with non-valvular atrial fibrillation and other risk factors for stroke (age over 65 years, history of hypertension, diabetes, heart failure, or left ventricular dysfunction). In patients over 75 years, the relative balance of risks and benefits of warfarin should be carefully assessed.

A - Warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) should also be considered for antithrombotic prophylaxis in patients with non-valvular atrial fibrillation who are aged under 65 and have a history of hypertension, diabetes, heart failure, or left ventricular dysfunction.

A - If warfarin is declined, or contraindicated by increased risk of bleeding, aspirin (75 to 300 mg/day) should be considered but is less effective than warfarin.

C - Warfarin prophylaxis should be considered in patients with atrial fibrillation and heart valve disease or prosthesis, thyrotoxicosis, intracardiac thrombus, or non-cerebral thromboembolism.

Cardioversion

C - Cardioversion of atrial fibrillation should be considered in selected patients.

C - Patients with very recent onset atrial fibrillation require immediate assessment and treatment with heparin.

C - If it is certain that atrial fibrillation has been present for two days or less, cardioversion should be attempted electrically or pharmacologically. Warfarin therapy is not required in these patients if cardioversion is successful.

B - If atrial fibrillation has been present for more than two days, warfarin should be given to reduce the risk of thromboembolism for three weeks before cardioversion and continued for at least four weeks after cardioversion. (Note: the guideline development group recommends a target international normalized ratio of prothrombin time of 2.5, range 2.0 to 3.0.)

Other Cardiac Causes of Systemic Embolism

Rheumatic Mitral Valve Disease

C - Long-term warfarin prophylaxis (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) is recommended in patients with rheumatic mitral valve disease.

B - Long-term warfarin prophylaxis (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) is recommended in patients with rheumatic mitral stenosis with atrial fibrillation.

Mitral Valve Prolapse, Mitral Annular Calcification, and Isolated Aortic Valve Disease

C - Long-term warfarin prophylaxis (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) is recommended for patients with mitral valve prolapse, mitral annular calcification, or isolated aortic valve disease only in the presence of previous systemic embolism or atrial fibrillation.

Cardiomyopathies and Cardiac Failure

C - Long-term warfarin prophylaxis (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) is recommended for patients with dilated cardiomyopathy or cardiac failure only in the presence of previous systemic embolism or atrial fibrillation.

Mechanical Heart Valves

B - Patients with mechanical heart valves should receive long-term prophylaxis with warfarin.

C - A target international normalized ratio of prothrombin time of 3.5, range 3.0 to 4.5, has traditionally been recommended for patients with mechanical heart valves and is appropriate for first generation valves (e.g., Starr-Edwards, Bjork Shiley standard).

B - More recent studies support a reduction in target international normalized ratio of prothrombin time to 3.0, range 2.5 to 3.5, for patients with second generation mechanical heart valves (e.g., St. Jude, Medtronic, Monostrut).

A - Addition of aspirin or dipyridamole should be considered in patients who suffer systemic embolism despite adequate-intensity warfarin.

Bioprosthetic Heart Valves

C - Patients with bioprosthetic heart valves who have additional thrombotic risk factors should receive long term prophylaxis with warfarin (international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0).

A - Selected patients may receive aspirin as additional therapy.

Other patients with mitral bioprosthetic valves should receive:

A - Warfarin for 3 to 6 months (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0)

C - followed by long-term aspirin (300 mg/day).

C - In other patients with isolated aortic or tricuspid bioprosthetic valves, warfarin is recommended for three months only, in the absence of atrial fibrillation or a history of systemic embolism.

Ischaemic Heart Disease

Myocardial Infarction

A - It is strongly recommended that all patients with clinically suspected evolving acute myocardial infarction who are not already receiving aspirin should be given aspirin (150 to 300 mg).

A - In patients already taking aspirin, it should be continued at a dose of 150 to 300 mg/day.

A - It is strongly recommended that aspirin (75 to 300 mg) be continued long term in survivors of myocardial infarction.

A - Clopidogrel (75 mg/day) is an effective alternative in patients with contraindications to aspirin, or who are intolerant of aspirin.

A - Aspirin may be continued in heparinised patients with acute myocardial infarction, but should be discontinued in patients receiving warfarin for ischaemic heart disease.

A - It is strongly recommended that all patients with clinically suspected evolving acute myocardial infarction be considered for thrombolytic therapy.

A - Thrombolysis should be used concurrently with aspirin, which has an additive effect.

A - Heparin should not be used routinely in addition to aspirin in acute myocardial infarction, but reserved for patients at increased thromboembolic risk.

A - Patients with acute, established myocardial infarction at increased risk of systemic or pulmonary thromboembolism due to:

- Large anterior Q-wave infarction
- Severe left ventricular dysfunction
- Congestive heart failure
- History of systemic or pulmonary embolism or thrombophilia
- Echocardiographic evidence of mural thrombus
- Persistent atrial fibrillation
- Prolonged immobilization
- Marked obesity

should be considered for anticoagulation with full-dose heparin (target activated partial thromboplastin time ratio 2.0, range 1.5 to 2.5) followed (if indicated by continuing risk) with warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) for up to three months, depending upon the physician's estimate of the risk : benefit ratio in the individual patient.

A - In other patients with acute myocardial infarction, and in patients as defined above in whom the bleeding risks of full-dose anticoagulation are judged to outweigh the benefits, prophylaxis of venous thromboembolism with low-dose subcutaneous heparin (7,500 IU 12-hourly) for seven days or until ambulant, should be considered.

C - In patients in whom the bleeding risks of low-dose heparin are judged to outweigh the benefits, graduated elastic compression stockings or intermittent pneumatic compression should be considered for prophylaxis of venous thromboembolism.

A - For long term prophylaxis of arterial events following myocardial infarction, antiplatelet agents (usually aspirin) are usually preferred to warfarin because of their lower complexity, bleeding risk, and cost.

A - Long term warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) should be considered instead of aspirin in patients with persistent atrial fibrillation and heart failure or left ventricular dysfunction.

Unstable Angina

A - It is strongly recommended that all patients with clinically suspected unstable angina should receive aspirin (150 to 300 mg/day) as soon as possible.

A - This should be continued long term as prophylaxis of cardiovascular events (75 to 300 mg/day).

A - It is strongly recommended that all patients who are hospitalised with severe unstable angina should receive in addition to aspirin full-dose heparin (target activated partial thromboplastin time ratio 2.0, range 1.5 to 2.5), which should be maintained for 3-4 days, or until resolution of unstable angina.

A - Alternatively, low molecular weight heparin (enoxaparin or dalteparin) can be given.

Stable Angina

A - Patients with stable angina should receive aspirin (75 to 300 mg/day) long term as prophylaxis of cardiovascular events.

Coronary Angioplasty, Stents, and Bypass Grafts

A - Aspirin (300 mg/day) should be given as antithrombotic prophylaxis, starting at least two hours prior to angioplasty, or six hours following bypass grafting (unless contraindicated by bleeding) and continued long term (75 to 300 mg/day).

Peripheral Arterial Disease

Intermittent Claudication

A - Patients with intermittent claudication should receive aspirin (75 to 300 mg/day) long term as prophylaxis of cardiovascular events.

A - Clopidogrel (75 mg/day) is an effective alternative in patients with contraindications to aspirin, or who are intolerant of aspirin.

Critical Limb Ischaemia and Amputation

C - Hospitalised patients with chronic critical limb ischaemia should receive prophylaxis for venous thromboembolism with either subcutaneous low dose standard heparin (5,000 IU 8 hourly) or adjusted-dose warfarin (target therapeutic range of international normalized ratio of prothrombin time 2.0 to 3.0).

C - In patients with acute critical ischaemia, full-dose intravenous heparin (target activated partial thromboplastin time ratio 2.0, range 1.5 to 2.5) is standard practice.

A - In patients with peripheral arterial embolism and atrial fibrillation or other cardiac source of embolism, long-term prophylaxis with warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) is recommended.

A - In patients with acute critical limb ischaemia, local thrombolytic therapy should be considered.

Peripheral Angioplasty and Bypass Grafts

C - It is standard practice to give intravenous heparin during peripheral angioplasty, and to heparinise systemically during bypass graft surgery.

A - Aspirin (300 mg/day) should be given as antithrombotic prophylaxis of cardiovascular events, starting 6 hours following angioplasty or bypass grafting and continued long-term (75 to 300 mg/day).

A - Clopidogrel (75 mg/day) is an effective alternative treatment for long term prophylaxis in patients with contraindications to aspirin, or who are intolerant of aspirin.

Cerebrovascular Disease

Acute Stroke

C - The SIGN guideline "Management of Patients with Stroke, Part I: Assessment, Investigation, Immediate Management and Secondary Prevention" recommends that all patients with acute stroke should undergo computed tomography brain scanning as soon as possible-preferably within 48 hours-and no later than seven days. A local protocol for more urgent scans (e.g., patients receiving anticoagulant or recent thrombolytic therapy) should be available.

A - Early treatment with aspirin (150 to 300 mg/day) is recommended in acute ischaemic stroke, starting as soon as intracranial haemorrhage is excluded by computed tomography brain scanning, for risk reduction in death and cardiovascular events.

A - Routine use of unfractionated or low molecular weight heparin (even at low doses) in acute stroke is not recommended.

C - In patients at increased risk of venous thromboembolism, additional prophylaxis with graduated elastic compression stockings should be considered in all immobile patients following acute stroke.

C - Early institution or maintenance of anticoagulant therapy (with heparin or warfarin) in acute ischaemic stroke should be reserved for patients with a high risk of either venous thromboembolism (e.g., previous venous thromboembolism, thrombophilias) or recurrent thromboembolic stroke (e.g., rheumatic valve disease or mechanical heart valves, especially in the presence of atrial fibrillation) in whom these risks are judged to outweigh the increased risk of intracranial bleeding.

C - Urgent computed tomography brain scans are indicated in such patients, to exclude intracranial bleeding and predictors of haemorrhagic transformation such as major cerebral infarction. Careful control of both hypertension and the intensity of anticoagulants in such patients is also recommended to reduce the risk of intracranial bleeding.

Secondary Prevention after Acute Ischaemic Stroke or Transient Cerebral Ischaemic Attack

C - The SIGN guideline "Management of Patients with Stroke, Part I: Assessment, Investigation, Immediate Management and Secondary Prevention" recommends that local admissions policies should be agreed, as well as local protocols for referral to a fast-track assessment clinic for those with minor strokes or transient cerebral ischaemic attacks not requiring hospital admission, for identification and modification of risk factors and rapid administration of secondary prevention including antithrombotic treatments.

A - Antiplatelet therapy-normally aspirin (75 to 300 mg/day)-should be prescribed as early as possible for secondary prevention of stroke and other vascular events in patients who have sustained an ischaemic stroke (or transient cerebral ischaemic attack). In acute ischaemic stroke, the starting dose should be 150 to 300 mg/day.

Dipyridamole (200 mg twice daily in a sustained release preparation) should be considered for prevention of cardiovascular events following ischaemic stroke:

> A - As an alternative to aspirin in patients with contraindications to aspirin, or who are intolerant of aspirin; and
>
> C - In addition to aspirin, especially in patients with recurrent stroke or transient cerebral ischaemic attack despite aspirin.

A - Clopidogrel (75 mg/day) should be considered as an alternative to aspirin in suitable patients with contraindications to aspirin, or who are intolerant of aspirin, for prevention of cardiovascular events following ischaemic stroke.

A - In patients with atrial fibrillation, warfarin (target international normalized ratio of prothrombin time 2.5, range 2.0 to 3.0) should be used in preference to antiplatelet therapy to reduce the risk of a further ischaemic stroke because of its greater efficacy.

C - Warfarin should also be considered as secondary prophylaxis after cardioembolic stroke from valvular heart disease or recent myocardial infarction.

Carotid Endarterectomy

C - The SIGN guideline "Management of Patients with Stroke. II: Management of Carotid Stenosis and Carotid Endarterectomy" recommends that patients should continue on antiplatelet drugs throughout the perioperative period and should be heparinised during the procedure.

Recurrent Arterial Thrombosis or Embolism

A/C* - In patients with recurrent arterial thromboembolism despite aspirin or other antiplatelet agents, especially those with cardiac sources of embolism or thrombophilias, prophylactic warfarin (target international normalized ratio 2.5, range 2.0 to 3.0) should be considered, balanced against the increased risk of bleeding.

*This is a grade A recommendation for patients with atrial fibrillation or myocardial infarction; grade C for patients with peripheral arterial thrombosis.

C - In patients with recurrent arterial thrombosis or embolism despite warfarin at target international normalized ratio of prothrombin time of 2.5, range 2.0 to 3.0, either the addition of aspirin (75 mg/day), high-intensity warfarin (target international normalized ratio of prothrombin time 3.5, range 3.0 to 4.0), or (if there is further recurrence) high-intensity warfarin plus aspirin (75 mg/day) may be considered.

C - The increased risk of bleeding with such regimens should be considered.

Primary Prophylaxis of Myocardial Infarction in High Risk Patients

Aspirin

A - Aspirin (75 mg/day) should be considered for primary prophylaxis of myocardial infarction in men at high risk, (e.g., 2% per year) balanced against the increased risks of bleeding.

C - Aspirin (75 mg/day) should also be considered for primary prophylaxis of myocardial infarction in women at high risk, (e.g., 2% per year) balanced against the increased risks of bleeding.

Warfarin

A - Low-dose warfarin (target international normalized ratio of prothrombin time 1.6, range 1.3 to 1.9) is effective in primary prophylaxis of ischaemic heart disease in high risk men. However, the need for international normalized ratio of prothrombin time monitoring and the risk of bleeding, especially when combined with aspirin, render it less attractive than aspirin for routine antithrombotic primary prophylaxis.

Other Indications for Anticoagulant Therapy

Warfarin

A - Minidose warfarin (1 mg/day, no international normalized ratio of prothrombin time monitoring) is recommended for prophylaxis of thrombosis in central venous catheters.

A - Low-dose warfarin (target international normalized ratio of prothrombin time 1.6, range 1.3 to 1.9) is recommended for prophylaxis of thrombosis during chemotherapy in stage IV breast cancer.

Heparins

Unfractionated Heparin

A - In patients given full-dose unfractionated heparin therapy, routine monitoring of the activated partial thromboplastin time ratio (at least daily) and adjustment of heparin doses according to a local protocol, to achieve the target therapeutic range of anticoagulant effect (activated partial thromboplastin time ratio) is strongly recommended.

C - Each laboratory should standardise its own target range for activated partial thromboplastin time ratio.

C - The platelet count should be monitored in all patients receiving heparin for five days or more, to detect heparin-induced thrombocytopenia, as recommended by the Committee on Safety of Medicines.

C - If thrombocytopenia is detected, heparin should be stopped immediately, and alternative anticoagulation considered, e.g., with recombinant hirudin; the heparinoid, danaparoid (unlicensed indication in United Kingdom); or the defibrinating agent, ancrod (unlicensed indication in United Kingdom). Warfarin may be considered once the platelet count has recovered.

C - Monitoring of bone density may be considered in patients at high risk of osteoporosis.

Oral Anticoagulants

Reversal of Oral Anticoagulant Therapy in Patients with Bleeding or High International Normalized Ratio of Prothrombin Time

C - The most common cause of fatal or disabling bleeding in patients receiving anticoagulant therapy is intracranial or intraspinal bleeding. Any such patients who have head injury, headache (recent, severe), confusion, impaired consciousness, or focal neurological symptoms and signs should have urgent computed tomography scanning to detect such bleeding, followed by appropriate referral.

B - In patients with a high international normalized ratio of prothrombin time (>8.0) or other risk factors for bleeding, vitamin K_1 (0.5 mg intravenously or 5 mg orally) should be considered.

B - In patients with non-severe bleeding and a high international normalized ratio of prothrombin time, warfarin should be stopped for 1 to 2 days and vitamin K_1 (0.5 to 2 mg intravenously or 5 to 10 mg orally) should be considered.

B - In patients with life threatening haemorrhage, factor IX complex concentrate should be given at a dose of 50 IU/kg body weight: such therapy is more efficacious than fresh frozen plasma. If factor VII concentrate is available it should be given at a similar dose. In addition, intravenous vitamin K_1 should be given (5 mg, repeated as necessary).

Management of Oral Anticoagulant Therapy Before and After Surgery and Invasive Procedures

C - Possible measures to reduce this risk include:

- Urgent reversal of oral anticoagulant therapy
- Elective discontinuation of the oral anticoagulant, or dose reduction, to achieve a lower international normalized ratio of prothrombin time
- Substitution of heparin

Definitions:

Grades of Recommendations:

A. Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B. Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III)
C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Statements of Evidence

Ia
Evidence obtained from meta-analysis of randomized controlled trials.

Ib
Evidence obtained from at least one randomized controlled trial.

II a
Evidence obtained from at least one well-designed controlled study without randomization.

II b
Evidence obtained from at least one other type of well-designed quasi-experimental study.

III
Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV
Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

CLINICAL ALGORITHM(S)

Algorithms are provided for the initial management of clinically suspected deep vein thrombosis and for the management of clinically suspected pulmonary embolism.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The specific type of supporting evidence is explicitly identified in each section of the guideline.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Antithrombotic Therapy

- Recent overviews of controlled trials have suggested that antithrombotic prophylaxis in appropriate people at increased risk of thrombosis, and antithrombotic treatment in appropriate patients with acute thrombosis, not only reduces disability and mortality, but is also cost-effective. Routine antithrombotic therapy in selected, high-risk patients therefore appears to offer a major, cost-effective health gain in Scotland.

Antiplatelet Therapy

- Antiplatelet therapy, usually with aspirin, is clearly effective (and also cost-effective) in reducing death in acute myocardial infarction or acute ischaemic stroke and in the prevention of serious vascular events when given as secondary prophylaxis to patients with clinical evidence of arterial disease. It is also effective in prevention of stroke in selected patients with heart valve

disease, and in atrial fibrillation, and in primary prevention of myocardial infarction in men with multiple risk factors.

Anticoagulant Therapy

- Anticoagulant therapy, usually with heparin injections short term and/or oral anticoagulants (usually warfarin) long term, is also clearly effective in prevention of serious vascular events when given as prophylaxis to high-risk patients, or as treatment of acute arterial or venous thrombosis.

Thrombolytic Therapy

- Short term thrombolytic therapy with streptokinase, anistreplase, or tissue plasminogen activator (alteplase) has been shown in a recent overview of large randomised controlled trials to significantly reduce mortality and morbidity (including stroke and heart failure) when given to selected patients with evolving acute myocardial infarction.

POTENTIAL HARMS

Anticoagulation Therapy

- Full-dose anticoagulation is a common cause of major internal bleeding, including intracranial, gastrointestinal or retroperitoneal haemorrhage, which can be fatal.
- Oral anticoagulants may have interactions with commonly prescribed drugs. A checklist is provided in Table 8 of the original guideline document.
- Heparin. Heparin therapy for more than four months carries a high risk of osteopenia and bone fractures. Heparin-induced thrombocytopenia may also occur.
- Aspirin. Adverse effects of aspirin include allergy (e.g. bronchospasm); gastric irritation, ulceration and bleeding; constipation; renal failure; and bleeding at other sites (bruising, subconjunctival, and intracranial). The risk of haemorrhagic stroke is about 1 in 2500 patient-years. The risk of major gastrointestinal bleeding is 1:500 patient-years and is dose dependent above 300 mg/day. There is an increased risk of bleeding with the combination of aspirin and heparin.
- Dipyridamole. In a large prevention study, dipyridamole was associated with initial headache, and is contraindicated in uncontrolled angina, which it may exacerbate.
- Clopidogrel. Clopidogrel is associated with gastrointestinal bleeding and skin rash.

Vitamin K_1 for Anticoagulant Reversal

- Large doses given rapidly may result in facial flushing, chest tightness, cyanosis, and hypotension

Factor IX and Factor VII Concentrate for Anticoagulant Reversal

- Exposes patients to pooled blood product which rarely may transmit hepatitis B
- Risk of recurrent thromboembolism

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to and cautions with full-dose anticoagulant drugs:

Note: These depend on individual circumstances and are seldom absolute.

- Uncorrected major bleeding
- Uncorrected major bleeding disorder (e.g., thrombocytopenia, haemophilias, liver failure, renal failure)
- Uncontrolled severe hypertension (e.g., systolic >200 mm Hg or diastolic >120 mm Hg)
- Potential bleeding lesions (e.g., active peptic ulcer, oesophageal varices; aneurysm, proliferative retinopathy; recent organ biopsy; recent trauma or surgery to head, orbit, spine; recent stroke; confirmed intracranial or intraspinal bleed)

Heparin-specific contraindications:

- History of heparin-induced thrombocytopenia or thrombosis

Warfarin-specific contraindications:

- Pregnancy (usually)
- Homozygous protein C deficiency (risk of skin necrosis)
- History of warfarin-related skin necrosis
- Uncooperative/unreliable patients (long-term therapy)

Aspirin-specific contraindications and cautions:

- Contraindications to aspirin include: known allergy; age under 12 years (risk of Reye's syndrome); active peptic ulceration; history of recent intracranial bleeding; and bleeding disorders including haemophilia, von Willebrand's disease, thrombocytopenia and severe liver disease
- Cautions with aspirin include asthma, uncontrolled hypertension (risk of intracranial bleeding); and previous peptic ulceration (risk of gastrointestinal bleeding: proton pump inhibitors or H_2-receptor antagonists may be considered for prophylaxis). Combination therapy with aspirin and anticoagulants increases the risk of bleeding and should be avoided, except in situations of high thrombotic risk where the antithrombotic benefits of combination therapy are perceived to outweigh the risk of bleeding.
- About one third of patients with acute stroke cannot swallow safely, and are at risk of aspiration.

Dipyridamole-specific contraindications:

- Dipyridamole is contraindicated in uncontrolled angina, which it may exacerbate.

Cardioversion

- Cardioversion carries a moderate risk of systemic thromboembolism in patients who have been in atrial fibrillation for more than two days.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve.

These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

Significant departures from the national guideline as expressed in the local guideline should be fully documented and the reasons for the differences explained. Significant departures from the local guideline should be full documented in the patient's case notes at the time the relevant decision is taken.

The benefits and risks of thrombolysis in acute ischaemic stroke are being evaluated in large, randomised controlled trials: at present the balance is unclear. The use of thrombolytic therapy was not addressed in detail in the pilot edition of this guideline.

A Scottish national guideline has been issued for identification of risk of venous thromboembolism and prophylaxis in patients at increased risk during hospitalisation, pregnancy or the puerperium and was being revised in 1999. This use of anticoagulant therapy was therefore not addressed in the present guideline.

To avoid constant repetition, the words â œunless contraindicatedâ have not been included in every recommendation on the use of drug therapy in this guideline, but all recommendations should be interpreted as carrying this caveat. The balance of risks (bleeding) and benefits of antithrombotic therapies should be carefully assessed in the individual patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Antithrombotic therapy with antiplatelet or anticoagulant drugs is indicated in a wide range of disorders which carry an increased risk of venous, cardiac or arterial thromboembolism. The recommendations in this guideline should therefore be considered when developing several local guidelines:

- Management of venous thromboembolism (see section 2 of the original guideline document)
- Management of atrial fibrillation (see section 3 of the original guideline document)
- Management of other cardiac causes of systemic embolism (see section 4 of the original guideline document)
- Management of ischaemic heart disease (see section 5 of the original guideline document), peripheral arterial disease (see section 6 of the original guideline document), and cerebrovascular disease (see section 7 of the original guideline document)
- Management of oral anticoagulant therapy (see section 12 of the original guideline document)

Development of these local guidelines will require coordinated action by health boards, National Health System trusts, general practitioners, relevant hospital medical staff (cardiovascular physicians and surgeons, haematologists, radiologists, anaesthetists), pharmacists, nurses, and the Area Clinical Audit Committee.

Local guidelines should be discussed with and circulated to all relevant staff, and displayed in appropriate areas (primary care clinics, accident and emergency departments, relevant hospital clinics and wards, haematology departments, and pharmacies).

Specific information on the following items is provided in the original guideline document (Section 14): patient specific reminders at time of consultation or admission, continuing education, audit, inpatient anticoagulation, outpatient anticoagulation and provision of antithrombotic prophylaxis to patients who may benefit.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Antithrombotic therapy. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 1999. 70 p. (SIGN publication; no. 36). [186 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.]

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GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Comments were also received from Professor Tony Wildsmith

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All members of the Scottish Intercollegiate Guidelines Network (SIGN) guideline development groups are required to complete a declaration of interests, both personal and non-personal. A personal interest involves payment to the individual concerned, e.g., consultancies or other fee-paid work commissioned by or shareholdings in the pharmaceutical industry; a non-personal interest involves payment which benefits any group, unit or department for which the individual is responsible, e.g., endowed fellowships or other pharmaceutical industry support. SIGN guideline group members should be able to act as independently of external commercial influences as possible, therefore, individuals who declare considerable

personal interests may be asked to withdraw from the group. Details of the declarations of interest of any guideline development group member(s) are available from the SIGN executive.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline was issued in 1999 and will be considered for review in 2002.

Any updates to the guideline that result from the availability of new evidence will be noted on the Scottish Intercollegiate Guidelines Network (SIGN) Web site.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Scottish Intercollegiate Guidelines Network (SIGN) Web site:

- HTML format
- Portable Document Format (PDF)

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Quick reference guide: Antithrombotic therapy. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network, 1999 Mar. 2 p. Available in Portable Document Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site.
- SIGN 50: A guideline developer's handbook. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network, 2001 Feb. (SIGN publication; no. 50). Electronic copies available from the SIGN Web site.
- Appraising the quality of clinical guidelines. The SIGN guide to the AGREE (Appraisal of Guidelines Research and Evaluation) guideline appraisal instrument. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network, 2001. Available from the SIGN Web site.
- A background paper on the legal implications of guidelines. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 3, 2002. The information was verified by the guideline developer as of February 4, 2002.

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